

## **Description**

### **DRUG ADMINISTRATION SUPPORT SYSTEM**

#### **Technical Field**

- [1] The present invention relates to a drug administration support system, more particularly to a drug administration support system for supporting drug administration when drug should be administered to a seriously affected patient with due consideration paid to information about the functional failure of his/her kidneys and his/her blood filtering.

#### **Background Art**

- [2] The seriously affected patient who needs care in ICU is apt to be complicated with infection. Whether the patient is complicated with infection or not is a crucial factor in the determination of his/her prognosis. Generally, to protect against infection, antibacterial agents (including antibacterial agents for bacterial infection and antifungal agents for fungal infection) and antiviral agents are used. Thus, proper use of antibacterial agents will ensure a prospective prognosis for such a seriously affected patient. Namely, proper use of antibacterial agents will have a beneficial effect on the period of his/her hospitalization and the efficacy of his/her treatment. Since generally antibacterial agents are expensive in general, proper use of antibacterial agents will also be economically important.
- [3] The antibacterial agent is excreted from his/her kidneys or his/her liver. A larger number of antibacterial agents are excreted from the kidneys. Therefore, if it is required to administer an antibacterial agent to a patient, it is necessary to adjust the dose of the drug considering how badly his/her renal function is damaged. For such a seriously affected patient, prolonged blood filtering may be employed. Then, the antibacterial agent is also eliminated as a result of blood filtering. Thus, it is also necessary, if the antibacterial agent must be administered to the patient who receives blood filtering, to adjust the dose of the drug considering its elimination as a result of blood filtering process.

#### **Disclosure of Invention**

##### **Technical- Problem**

- [4] However, there is scarcely any guideline in the prior art to show how the dose of an antibacterial agent should be adjusted when it is administered during prolonged blood filtering. Namely, no guideline has paid due attention to the information about the functional disorders of kidneys that may vary in severity during prolonged blood filtering, and about the blood filtering process itself. In the treatment of a seriously affected patient, it is necessary to promptly determine a proper therapy. However,

since there is no reliable guideline upon which one can adjust the dose of an antibacterial agent for a patient dependent on prolonged blood filtering, it has not been possible to promptly determine a proper therapy (e.g., the dose of an antibacterial agent) for such a patient.

- [5] In order to provide a solution to the above problem, it is an object of the present invention to provide a drug administration support system for supporting the proper and prompt administration of a drug to a seriously affected patient with due consideration paid to the information about the functional failure of the kidneys and the blood filtering.

### Technical- Solution

- [6] The inventive drug administration support system is a drug administration support system comprising: storing means for storing blood filtering information, biological information and drug information; calculating means for calculating a total clearance of the drug with due consideration paid to the renal function failure and blood filtering on the basis of the blood filtering information, biological information, and drug information; and displaying means for displaying the obtained total clearance.

- [7] According to the inventive system configured as above, since the total clearance of a drug is calculated with due consideration paid to the renal functional failure and blood filtering, it is possible to provide a guideline necessary for the prompt determination of a therapy suitable for treating a seriously affected patient. By determining the dose of a drug based on the total clearance derived from the renal clearance due to renal excretion during blood filtering and the blood filtering clearance due to CHF, it is possible to properly and promptly administer the drug to a seriously affected patient with due consideration paid to the information about his/her renal functional failure and blood filtering.

- [8] In the inventive drug administration support system, it is preferable that said calculating means calculates the total clearance of the drug by the following formula:  

$$CL_t = k \times CL_{cr} + (1 - T/100) \times Q_w \times (1 - f/100) + CL_a$$
 where  $CL_t$ (ml/min) represents a total clearance during the blood filtering,  $k$  and  $T$  are constants fixed for individual drugs,  $k$  represents a coefficient for converting from the creatinine clearance to the drug clearance,  $T$  represents a protein binding rate of the drug,  $Q_w$ (ml/min) is the set value in the blood filtering,  $CL_{cr}$ (ml/min) represents a renal creatinine clearance,  $f$  represents a filter clogging removal efficiency reduction index, and  $CL_a$ (ml/min) represents a clearance of absorbing the drug to the blood filter.

- [9] In the inventive drug administration support system it is preferable that the creatinine clearance is calculated from the concentration of creatinine in serum by the following formula:

$$CL_{Cr} = [BW \times (140 - Y) / (72 \times Cr)] \times M$$

where BW (kg) represents the body weight, Y (y.o.) represents an age, Cr (mg/dl) represents the concentration of creatinine in serum, and M (mg/dl) represents a coefficient (male, 1; female, 0.85).

- [10] In the inventive drug administration support system it is preferable that the total clearance of the drug is the sum of the renal clearance of the drug and the blood filtering clearance of the drug.
- [11] In the inventive drug administration support system it is preferable that said displaying means displays a guideline by a level bar as the indication of the renal creatinine clearance.
- [12] In the inventive drug administration support system it is preferable that said drug is the renal secretion drug.
- [13] The program according to the invention is preferably a program operable in a computer, the program comprising the steps of: extracting stored blood filtering information, biological information and drug information from a memory; and calculating a total clearance of the drug with due consideration paid to the renal function failure and blood filtering on the basis of the blood filtering information, biological information, and drug information.

#### **Advantageous Effects**

- [14] Since the inventive drug administration support system calculates the total clearance of a drug with due consideration paid to the renal function failure and blood filtering on the basis of blood filtering information, biological information, and drug information, it is possible to properly and promptly administer the drug to a seriously affected patient with due consideration paid to the information about his/her renal function failure and blood filtering.

#### **Description Of Drawings**

- [15] Fig. 1 is a block diagram for illustrating the outline of a drug administration support system representing the embodiment of the invention.
- [16] Fig. 2 shows a display screen of the drug administration support system representing the embodiment of the invention.
- [17] Fig. 3 shows another display screen of the drug administration support system representing the embodiment of the invention.
- [18] Fig. 4 shows yet another display screen of the drug administration support system representing the embodiment of the invention.
- [19] Fig. 5 shows yet another display screen of the drug administration support system representing the embodiment of the invention.

#### **Best Mode**

- [20] The embodiments of the present invention will be described in detail below with reference to the attached figures. The embodiments are described below in case that an antibacterial agent is used as the drug which is largely excreted from kidneys, but the drug is not necessarily limited to kidney-excreted antibacterial agents, but may include, in addition to other kidney-excreted agents such as antiviral agents, liver-excreted agents.
- [21] The inventive drug administration support system is characterized in that it provides a guideline for the proper dose of a drug on the basis of the total clearance from the renal clearance due to renal excretion during continuous hemofiltration (CHF hereinafter) and from the blood filtering clearance due to CHF.
- [22] The total clearance of an antibacterial agent can be expressed by the sum of the renal clearance of the antibacterial agent and its CHF clearance (equation (1)):  

$$CL_t = CL_r + CL_{chf} \dots (1)$$
where  $CL_t$  (ml/min) represents the total clearance of an antibacterial agent during CHF,  $CL_r$  (ml/min) the renal clearance of the antibacterial agent, and  $CL_{chf}$  (ml/min) the CHF clearance of the antibacterial agent.
- [23] The CHF clearance of the antibacterial agent can be expressed by the sum of the clearance of the antibacterial agent as a result of its transfer into CHF liquid waste and the clearance of the antibacterial agent due to its adsorption to CHF filter (equation (2)):  

$$CL_{chf} = CL_w + CL_a \dots (2)$$
where  $CL_w$  (ml/min) represents the clearance of the antibacterial agent as a result of its transfer into CHF liquid waste, and  $CL_a$  (ml/min) the clearance of the antibacterial agent due to its adsorption to CHF filter.
- [24] The clearance of the antibacterial agent as a result of its transfer into CHF liquid waste ( $CL_w$ ) can be determined from the filtration coefficient of the antibacterial agent and the flow amount of CHF liquid waste:  

$$CL_w = SC_t \times Q_w \dots (3)$$
where  $SC_t(-)$  represents the filtration coefficient of the antibacterial agent and  $Q_w$  (ml/min) the flow amount of CHF liquid waste.
- [25] The filtration coefficient of the antibacterial agent can be expressed by equation (4) and the filtration coefficient of the free component of the antibacterial agent can be expressed by equation (5):  

$$SC_t = C_{wt}/C_t \dots (4)$$

$$SC_f = C_{wf}/C_f \dots (5)$$
where  $C_{wt}$  ( $\mu\text{g/ml}$ ) represents the concentration of the antibacterial agent in the liquid waste, and  $C_t$  ( $\mu\text{g/ml}$ ) the concentration of the antibacterial agent in blood.  $SC_f(-)$  represents the filtration coefficient of the free component of the antibacterial agent,

Cwf ( $\mu\text{g/ml}$ ) the concentration of the free component of the antibacterial agent in the liquid waste, and Cf ( $\mu\text{g/ml}$ ) the concentration of the free component of the antibacterial agent in blood.

- [26] The relation of the concentration of the antibacterial agent in blood (Ct) with the concentration of the free component of the antibacterial agent in blood (Cf) can be expressed using a protein binding rate T by equation (6):

$$Cf = Ct \times (1 - T/100) \dots (6)$$

where T(%) represents the fraction of the antibacterial agent bound to protein.

- [27] Since the free component of the antibacterial agent has a molecular weight of several hundreds to one thousand and several hundreds Daltons, the concentration of the free component of the antibacterial agent in blood will be approximately equal to the concentration of the free component of the antibacterial agent in CHF liquid waste, if the cut-off point of the filter used in CHF is about twenty thousands Daltons. Accordingly,

$$SCf \approx 1 \dots (7)$$

From equations (4) and (7),

$$Cwf = Cf \dots (8)$$

- [28] Since the component (mainly albumin) of the antibacterial agent bound to protein is hardly eliminated through pores on the lateral walls of the filter into the liquid waste,

$$Cwt = Cwf \dots (9)$$

Accordingly, from equations (8) and (9),

$$Cwt = Cf \dots (10)$$

Then, from equations (3), (5), (6) and (10),

$$CLw = (1 - T/100) \times Qw \dots (11)$$

- [29] The filter consists of hollow fibers. Each hollow fiber becomes increasingly clogged as time goes after the start of CHF because of adsorption of solutes to the fiber wall, and the formation of polarization layers and gel layers on the wall. If the filter is clogged, clearance of the antibacterial agent as a result of transfer into the liquid waste will be reduced. If a filter clogging removal efficiency reduction index f (%) is introduced to define the reduced efficiency of the elimination of the antibacterial agent into the liquid waste as a result of filter clogging of the hollow fibers, the clearance of the antibacterial agent into the liquid waste (CLw') can be expressed by equation (12):

$$CLw' = CLw \times (1 - f/100) \dots (12)$$

Then, from equations (11) and (12),

$$CLw' = (1 - T/100) \times Qw \times (1 - f/100) \dots (13)$$

- [30] The renal clearance of the antibacterial agent (CLr) is determined based on the renal creatinine clearance (CLcr) by equation (14) below:

$$CLr = k \times CLcr \dots (14)$$

where CLcr (ml/min) represents the renal creatinine clearance, and k (-) a coefficient converting the creatinine clearance to the antibacterial agent clearance.

- [31] From equations (12), (13) and (14), the clearance during CHF can be determined by equation (15) below:

$$CL_t = k \times CL_{cr} + (1-T/100) \times Q_w \times (1-f/100) + CL_a \dots (15)$$

where k and T are constants fixed for individual antibacterial agents, k represents a coefficient for converting the creatinine clearance to the drug clearance, T represents the fraction of the drug bound to protein, Q<sub>w</sub> is a set value during CHF, and CLcr is calculated from the serum creatinine concentration by equation (16) below.

$$CL_{cr} = [BW \times (140-Y)/(72 \times Cr)] \times M \dots (16)$$

where BW (kg) represents the body weight, Y (y.o.) the age, Cr (mg/dl) the concentration of creatinine in serum, and M (mg/dl) a coefficient (male, 1; female, 0.85).

- [32] With regard to equation (15), f increases with time while CL<sub>a</sub> decreases with time. As is disclosed in the Japanese Patent Application No. 2003-179911 (filed on June 27, 2003) submitted by the present inventors (the Application is incorporated in its entirety herein by reference), f at a given time can be determined by multiplying the filter clogging index (S) with the correction coefficient (h) as is represented by equation (17) below:

$$f = h \times S \dots (17)$$

where h(-) represents the correction coefficient and S(%) the filter clogging index.

- [33] CL<sub>a</sub> at a given time is determined by the type of filter, type of the antibacterial agent, dose of the antibacterial agent, blood concentration of protein to which the antibacterial agent is bound, body weight, elapsed time, flow of blood (total volume of blood passing through the filter), and flow of filtrate (total volume of the filtrate). Each time the filter is replaced, the total adsorption of the antibacterial agent to the filter should be determined anew. It often occurs that at the early phase of hemofiltration, the filter becomes saturated in the adsorption of an antibacterial agent thereto, and CL<sub>a</sub> becomes null. However, as long as an antibacterial agent continues to be adsorbed to a filter or its single dose is low because of its being active at a low concentration, the dose of the antibacterial agent should be adjusted with allowance made for its CL<sub>a</sub>.

- [34] Since the inventive system takes into account parameters changing with time such as f-value and CL<sub>a</sub>, it is possible to provide a guideline necessary for promptly determining a proper therapy for a seriously affected patient whose condition varies from one moment to another. As described above, according to the inventive system, since a guideline for the proper prescription of the dose of a drug is provided based on the total clearance of the drug derived from the renal clearance due to renal excretion during CHF and the blood filtering clearance due to CHF, it is possible to properly and promptly administer a drug to a seriously affected patient with due consideration paid

to the information about his/her renal function failure and blood filtering.

- [35] Next, will be described a case in which an inventive drug administration support system is used for providing a guideline for the proper prescription of the dose of a drug to be administered to a seriously affected patient. Fig. 1 is a block diagram for illustrating the general configuration of a drug administration support system representing an embodiment of the invention.
- [36] The drug administration support system 1 is mainly composed of a control portion 11 for controlling the entire system, a calculation portion 12 for calculating the total clearance of a drug from the above equation based on drug information, blood filtering information and biological information, a display control portion 13 for converting the total clearance, drug information, blood filtering information and biological information into a displayable format, a memory 14 for storing the drug information, blood filtering information and biological information, a display 15 for displaying the information converted into a displayable format, and an input portion 16 through which the user can feed necessary information to the system.
- [37] The blood filtering information concerns the type of filter, area of membrane, material, flow of blood, weight of filtrate, flow of dialysate, flow of replacement fluid, flow of drain, start date of filtration, etc for prolonged blood filtering. The blood filtering information is displayed on a blood filtering information display screen 21 as shown in Fig. 2. The biological information concerns the age, sex, weight and height of the patient and his/her results of laboratory test, etc. The biological information is displayed on a biological information display screen 22 as shown in Fig. 3. The drug information concerns the commercial name, class and generic name of the drug to be used, date and frequency of administration, etc. Specifically, suitable drugs may include antibacterial agents. The drug information is displayed on a drug selection screen 23 as shown in Fig. 4.
- [38] The blood filtering information and biological information may be transmitted from a separate device such as a crit line monitor. The drug information is fed via the input portion 16. However, the present invention is not limited to the above configuration. The blood filtering information and biological information may be fed via the input portion 16. Alternatively, the drug information, blood filtering information and biological information may be fetched from a separate device, for example from a drug database.
- [39] On the drug selection screen 23, the user can select any one of the three options by clicking one of the buttons attached to the three options which permit the display of drug information, display of simulated drug concentration transition, and support of drug administration. If the user clicks the button for the display of drug information, the system fetches, for the drug fed via the drug selection screen, necessary in-

formation (e.g., usage, contraindications, warnings, etc.) from a database storing the data of drugs, and displays it. If the user clicks the button for the display of simulated drug concentration transition, the system displays drug concentration transition over time based on simulation as well as on real measurements in a graphical form. If the user clicks the button for the support of drug administration, the system displays a guideline for drug administration based on the total clearance of the drug as will be described later.

- [40] When the system actually displays a guideline for drug administration based on the total clearance of a drug for a patient on CHF, the blood filtering information, biological information and drug information are stored in memory 14. The blood filtering information is converted by display control portion 13 into a predetermined format and displayed on blood filtering information display screen 21. The biological information is converted by display control portion 13 into a predetermined format and displayed on biological information display screen 22. The drug information is converted by display control portion 13 into a predetermined format and displayed on drug selection screen 23. The blood filtering information and biological information are transmitted from a separate device. The drug information is fed via the input portion 16.
- [41] The calculation portion 12 derives information necessary for calculation from the blood filtering, biological and drug information stored in memory 14, and calculates the total clearance based on the aforementioned equations. The thus obtained total clearance value is stored in memory 14.
- [42] The total clearance value is converted by display control portion 13 with a predetermined format and displayed on the drug administration support screen 24 as shown in Fig. 5. On the drug administration support screen 24, a guideline of the dose of a drug is offered by a level bar as the indication of renal creatinine clearance. Specifically, as seen from Fig. 5, the renal clearance and CHF clearance of the drug are displayed in a graphical form, and the guideline of the dose of the drug is offered which varies dependent on the level of total clearance. Accordingly, the user can readily recognize the meaning of the guideline by referring to the total clearance displayed as a graph. The drug administration support screen 24 may further include, as needed, additional information necessary for the proper administration of a drug.
- [43] Next, description will be given about a real case in which the total clearance is calculated and displayed on a screen such as that of Fig. 5. Then, the system will perform following procedures. If a kidney-excreted drug such as an antibacterial agent is administered to a patient during CHF, the dose of the drug is often adjusted based on the renal creatinine clearance (CL<sub>cr</sub>) which is calculated from the concentration of creatinine in serum by the above equation (16). Incidentally, in this embodiment, the